

immunization should be carried out with DTP. Three intramuscular injections each 0.5 mL, 4 to 6 weeks apart, boosters at 2 to 5 years of age. Not recommended above the age of 5 years.

b. *Contraindications.* (1) Respiratory or other acute infections; (2) cerebral damage; (3) severe febrile reactions; (4) encephalitic reaction to vaccine; and (5) persons on corticosteroid treatment.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A study reported in *The British Medical Journal* (Ref. 1) used this

product. Table 1 in the study states a "plain suspension" was used, while this product is adsorbed. Vaccine used in the study had  $10,000 \times 10^6$  organisms per mL. Dosage was 1, 2, 3 mL at monthly intervals for total of  $60,000 \times 10^6$  organisms. Children 6 to 18 months were immunized. Vaccine lot D 231 was tested in 630 subjects with 655 controls; vaccine lot A 236 was tested in 1,056 subjects with 993 controls. The following table is a summary of the data presented in the study.

TABLE 1

Vaccine	Attack rate/1,000 child months		Percent attack rate in home exposure		Percent attack rate in other exposures	
	Vac.	Univac.	Vac.	Univac.	Vac.	
D 231	0.97	7.04	7.3	79.5	4.6	36.7
A 236	0.60	6.48	8.9	90.0	3.8	34.8

Comparison of attack rates in the two groups indicates that the vaccine provided approximately 80 to 85 percent protection against pertussis.

b. *Safety.* One child in five was visited 24 to 72 hours after each injection. No severe local or general reactions were observed although a number developed temperature rises within 24 hours.

No specific data are provided for the present product.

c. *Benefit/risk ratio.* The benefit-to-risk assessment is favorable.

4. *Critique.* The human efficacy data would appear to prove the value of this product, but the studies were based upon a differing dosage schedule of a plain, not adsorbed, vaccine (with a greater dosage of antigen). Extrapolation of the British Medical Research Council data to the present product may not be entirely justified but provides some of the best available data.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

#### Pertussis Vaccine Manufactured by Dow Chemical Company

1. *Description.* No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* In the absence of any data for the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

5. *Recommendations.* The Panel recommends that this product be placed in Category III and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

#### Pertussis Vaccine, Fluid, Manufactured by Eli Lilly and Company

1. *Description.* Pertussis vaccine, fluid, is an unwashed suspension of killed *Bordetella pertussis* cells grown in modified Cohen-Wheeler medium. The methods of killing and detoxification are not given. The product is preserved with 1:10,000 merthiolate, and the total human immunizing dose (1.5 mL) contains the equivalent of 12 antigenic units of the U.S. standard pertussis vaccine.

2. *Labeling*—a. *Recommended use/indications.* For active immunization

against pertussis. The package circular recommends that three 0.5 mL doses be administered subcutaneously at intervals of 3 to 4 weeks for primary immunization. A booster or "optimum stimulating" dose of 0.25 to 0.5 mL is recommended for administration approximately 1 year after primary immunization.

b. *Contraindications.* Elective immunization should be postponed in the presence of acute infections. Postvaccinal neurologic disorders contraindicate further injections. Personal or family history of central nervous system damage or convulsions is an indication for fractional dosages. It is noted that corticosteroids may interfere with the immune response.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific studies on this product are presented or cited. Claims for efficacy appear to be based largely on demonstrated correlation of potency in mice and protective efficacy in children (Ref. 2).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data on this product were presented. The manufacturer's submission indicated no consumer complaints over a 5-year period.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

d. *Labeling.* No mention is made of the desirability of using DTP for immunization of most infants.

Although postvaccinal neurological disorders including convulsions are listed as a contraindication to further use, the labeling goes on to recommend fractional dosage. This is contradictory.

The reference to avoiding use of the vaccine when polio is present in the community is outdated and should be deleted.

4. *Critique.* It should be noted that this is a whole-cell pertussis vaccine, and, as such, differs significantly from that used in this manufacturer's DTP, in which a "solubilized" bacterial fraction is employed.

While no specific studies on this product are presented or cited, claims for efficacy are justifiably based largely on the demonstrated correlation of potency as determined by the intracerebral mouse protection test and protective efficacy in children.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and

effectiveness for this product. Labeling should be revised in accordance with the recommendations of this Report.

**Pertussis Vaccine, Fluid, Manufactured by Lederle Laboratories Division, American Cyanamid Co.**

1. *Description.* No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

**Pertussis Vaccine, Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.**

1. *Description.* The manufacturer did not provide a description of the monovalent pertussis vaccine for which a license is maintained. Instead a submission for pertussis vaccine combined with diphtheria and tetanus toxoids is provided, and includes details of the production of the pertussis component. The manufacturer has released no monovalent pertussis vaccine for 12 or more years.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This pertussis vaccine prepared for the combined product meets Federal requirements.

(2) *Human.* The evidence for efficacy in humans comprises a study from 1950 in which 75 infants were immunized with this pertussis vaccine combined

with diphtheria and tetanus toxoids (Ref. 3). In this study, satisfactory pertussis immunization was achieved as determined serologically.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* When employed in combination with diphtheria and tetanus toxoids no serious reaction occurred in 100 infants immunized.

c. *Benefit/risk ratio.* The benefit-to-risk assessment cannot be determined for this product in the monovalent form.

4. *Critique.* This vaccine has not been marketed for more than 12 years and no specific data related to this product in the monovalent form were provided. Except for rare instances of community outbreaks of pertussis in which it might be desirable to administer monovalent pertussis vaccine, these products do not enjoy wide usage.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

**Pertussis Vaccine Manufactured by Parke, Davis & Co.**

1. *Description.* A sterile saline suspension of centrifuged and resuspended "selected" strains of Phase 1 *Bordetella pertussis* is grown on semi-synthetic liquid medium. The organisms are inactivated by incubation in the presence of formaldehyde. Thimerosal 0.01 percent is added as a preservative. Total dose contains 12 units of pertussis vaccine. The product is currently not marketed.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for "rapid primary immunization" of infants and children against pertussis—to be followed ordinarily by immunization with DTP in order to complete immunization against the other antigens in this combination; 3 doses of 0.5 mL each are given subcutaneously at 3- to 4-week intervals or, if rapid immunization is indicated, at 1-week intervals. However, the longer interval is probably better. A booster dose of 0.5 mL is recommended 1 year after basic immunization and at 3 to 6 years of age or in the presence of actual or potential exposure to the disease in children under 6 years.

b. *Contraindications.* Defer immunization in presence of cerebral damage, active infection, or acute respiratory disease. Discontinue if encephalopathic symptoms appear. Give

smaller graduated doses if a systemic reaction occurs.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Antibody response data of 1961 to 1963 (Ref. 4) appear satisfactory, but it is not clear that this can be extrapolated to the current product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on this particular product are presented. No market experience is reported.

c. *Benefit/risk ratio.* This cannot be judged in view of the absence of data on reactions to this particular product.

4. *Critique.* This is a fluid pertussis vaccine made by the pioneer firm in developing pertussis vaccine in the United States, but differing from their classical "Sauer vaccine" in that it is made in-liquid medium instead of on a solid Bordet-Gengou medium. No data are provided on human safety or human antibody responses; the last package insert is dated 1966. This is an inactive product. Only illegible photostats of labels are presented. The emphasis in the package insert on using the fluid vaccine for "rapid immunization" cites no reference supporting this recommendation.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed, and consequently there are insufficient data on labeling, safety, and effectiveness.

**Pertussis Vaccine Adsorbed Manufactured by Parke, Davis & Co.**

1. *Description.* This is an aluminum phosphate adsorbed pertussis vaccine, currently not on the market. It contains 15 opacity units per 0.5 mL dose and 4 antigenic units per dose. It is centrifuged, resuspended in 0.9 percent saline, mixed with aluminum phosphate, and 0.01 percent thimerosal is added.

2. *Labeling*—a. *Recommended use/indications.* This vaccine is recommended as an efficient method of immunizing infants and children against whooping cough when a monovalent immunizing agent is indicated; these circumstances are not defined further. Recommendations for routine immunization are standard.

b. *Contraindications.* The usual contraindications are noted, particularly with regard to children having any history or signs of encephalopathy.

3. *Analysis*—a. *Efficacy*—(1) *Animal*. This product meets Federal requirements.

(2) *Human*. Evidence of direct human efficacy is not presented.

b. *Safety*—(1) *Animal*. This product meets Federal requirements.

(2) *Human*. Data are reported in the submission (Ref. 4) concerning 27 children who received the adsorbed pertussis vaccine in 1967, of whom 5 had systemic reactions as measured by fever. No other information regarding human safety is included.

c. *Benefit/risk ratio*. The data provided are inadequate to make a determination.

4. *Critique*. This is an aluminum phosphate adsorbed pertussis vaccine, currently not on the market, but one that would meet current standards for animal safety. Whether it is efficacious and safe in humans is not possible to determine from the data submitted.

5. *Recommendations*. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed, and consequently there are insufficient data on labeling, safety, and effectiveness.

#### **Pertussis Vaccine Manufactured by Texas Department of Health Resources**

1. *Description*. This product is prepared from Phase I stains of *Bordetella pertussis* and is an unwashed suspension of the organisms in physiological sodium chloride solution, killed, and preserved by thimerosal in final concentration of 1:10,000.

The vaccine is tested for antigenic potency by the mouse-protection test, and the degree of protection must equal or exceed that of the U.S. standard pertussis vaccine. The total immunizing dose contains 12 units.

2. *Labeling*—a. *Recommended use/indications*. This preparation is recommended for active immunization of children. Three doses of 1.0 mL of the vaccine are given deep subcutaneously at 3- to 4-week intervals. The labeling also recommends that booster doses of 0.3 or 1.0 mL be given at about 2 years of age, again at the age of 5 or 6 years, during epidemics, and after known exposure to the disease. Pertussis vaccine plain is not recommended for immunization of children under 6 months of age. "In this group, the pertussis vaccine with the mineral adjuvant is the material of choice."

b. *Contraindications*. These include any respiratory or other acute infections. The presence of cerebral damage in an infant is an indication for delay in

immunizations. It is advised that in such children and in those experiencing severe febrile reactions with or without convulsions, immunization procedures should be delayed and/or given in fractional doses. This is partly incorrect, and the label should state that in children who experience shock, convulsions, encephalopathy, excessive screaming, or thrombocytopenia, after vaccinations with a pertussis vaccine, no further injections of any pertussis vaccine should be given.

3. *Analysis*—a. *Efficacy*—(1) *Animal*. This product meets Federal requirements.

(2) *Human*. No data are provided relative to this particular product, but reference is made to the general data accumulated in the United States, including a chart of decreasing incidence of pertussis in Texas over time (Ref. 5).

b. *Safety*—(1) *Animal*. This product meets Federal requirements.

(2) *Human*. This product has been produced since 1945. The number of released doses is not given, but it is stated that there is a lack of reaction reports to the single fluid antigen in Texas.

c. *Benefit/risk ratio*. The benefit-to-risk assessment appears to be satisfactory but is not well documented.

d. *Labeling*. There are two flaws in the label as described above:

(1) The lack of a clear statement that DPT is usually the vaccine of choice for routine immunization of children.

(2) No mention of convulsions, shock, encephalopathy, excessive screaming, or thrombocytopenia following a dose of pertussis vaccine (plain or combined) as an absolute contraindication for further immunization of pertussis (but immunization can usually be contained with DT).

4. *Critique*. It is not known how many doses of this product have been distributed. The immunization dose is 1 mL instead of ½ mL, which is unusual. The labeling is partly misleading as described above.

5. *Recommendations*. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

#### **Pertussis Vaccine Manufactured by Wyeth Laboratories, Inc.**

1. *Description*. No data have been provided by the manufacturer for the monovalent pertussis vaccine for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications*. No labeling was provided.

b. *Contraindications*. No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal*. No information was provided.

b. *Safety*—(1) *Animal*. No information was provided.

(2) *Human*. No information was provided.

c. *Benefit/risk ratio*. The benefit-to-risk assessment of this product cannot be determined.

4. *Critique*. In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must recommend revocation of licensure for administrative reasons.

5. *Recommendations*. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

#### **References**

- (1) Bedson, S. P., W. C. Cockburn, et al., "Prevention of Whooping Cough by Vaccination by a Medical-Research Council Investigation," *The British Medical Journal*, 1:1463-1471, 1951.
- (2) BER Volume 2046.
- (3) BER Volume 2076.
- (4) BER Volume 2005.
- (5) BER Volume 2101.

#### **Generic Statement**

Diphtheria and Tetanus Toxoids and Pertussis Vaccine (DTP) (See Generic Statement for Monovalent Components)

#### *Description*

This product is a combination of diphtheria and tetanus toxoids with pertussis vaccine, intended for the primary immunization and maintenance of immunity against diphtheria, tetanus, and pertussis in children 6 years of age or less.

#### *Production*

DTP comprises diphtheria and tetanus toxoids and pertussis vaccine prepared in a manner usually similar to that of the monovalent preparations, and combined into a single preparation. Both fluid and adsorbed products are currently licensed and used in the United States. One manufacturer produces a partially purified fraction of pertussis organisms.

#### *Use and Contraindications*

DTP is recommended for the primary immunization of infants and children 6

years of age or younger. Recommended schedules are provided by the Advisory Committee on Immunization Practices of the United States Public Health Service, the American Academy of Pediatrics, and the American Public Health Association.<sup>1</sup> Primary immunization comprises a series of 4 doses administered subcutaneously or intramuscularly and the adsorbed preparations should be given intramuscularly.

The Advisory Committee on Immunization Practices recommends that the first 3 doses be given at 4- to 6-week intervals with a fourth dose approximately 1 year after the third injection. Ideally, immunization should begin at 2 to 3 months of age or at the time of a 6-week checkup if that is more practical. It is advisable not to administer DTP to individuals 7 years of age or older because untoward reactions to the pertussis component may be severe.

Contraindications are of two general types. The first of these is a severe hypersensitivity response to a prior injection. The other is a definite or suspected untoward reaction to the pertussis component of DTP. (See Generic Statement for Pertussis Vaccine.)

As with the individual components, the administration of DTP should be deferred in the presence of a febrile illness, because of possible confusion as to the etiology of persistent fever. Individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time.

#### Safety

There is no evidence that the combination of tetanus and diphtheria toxoids with pertussis vaccine synergistically increases the likelihood of adverse reactions over that observed with the individual components.

The toxoid components are tested for detoxification and the final product must be tested for safety according to Federal requirements.

#### Efficacy

Laboratory and animal procedures for determining the potency of DTP, as specified by Federal requirements, are carried out. In the case of the pertussis component of DTP the mouse protection test affords a reasonably satisfactory

means of correlating an animal model with protection in humans (See Generic Statements for Monovalent Products). An immunologic advantage of DTP over the monovalent toxoids is that the pertussis component exerts some adjuvant effect on diphtheria and tetanus toxoids.

#### Special Problems.

1. The available information indicates that the components of DTP, singly or in combination, are more immunogenic in the adsorbed preparations than in the fluid products. It is therefore questioned by some whether continued production and use of fluid toxoids and vaccines have any advantage.

2. DTP has been one of the most widely used vaccines. Most experiences, therefore, with adverse reactions to the components have been derived from experience with the combined product rather than from the monovalent preparations. Problems with individual components are similar to those of the monovalent products and may be summarized as follows. (See Generic Statements for Monovalent Diphtheria and Tetanus Toxoids and Pertussis Vaccine for detailed discussion.)

a. *Diphtheria*. Diphtheria toxoid, fluid or adsorbed, single or in combination, even with the adjuvant effect of pertussis vaccine, is not as effective an immunizing agent as might be desired. Evidence for this includes the occasional occurrence of diphtheria in immunized individuals and infections with nontoxigenic strains. Furthermore, there is concern about the permanence of immunity and the effectiveness of the present booster program in the light of the decreased frequency of exposure to the organism in the community, a phenomenon that may have provided repeated natural enhancement of immunity in the past. Whether increased purification of the toxoid may reduce immunogenicity is also unknown. Other problems with the diphtheria component include nonspecific reactivity and the lack of an animal model that would obviate field testing of improved toxoids in humans.

b. *Tetanus*. There is evidence that recent changes in manufacturing procedures, designed to reduce reactivity, may have lowered the immunizing potency of current tetanus toxoids compared to those in use 30 years ago.

c. *Pertussis*. Because the pathogenesis of pertussis and the biology of *Bordetella pertussis* are poorly understood, knowledge of the immune response and the pathophysiology of both the disease and immunization is limited. Without better definition of the

components of the organism and their relation to disease and immunity, attempts to improve immunogenicity and reduce reactivity of pertussis vaccines are seriously hampered. Additional unknown facts about pertussis and pertussis immunization that requires study include the true incidence of the disease, whether present vaccines need to reflect currently prevalent strains of *Bordetella pertussis*, the permanence of vaccine-induced immunity, and the true frequency and significance of the various untoward reactions. Furthermore, laboratory testing procedures used in the production and evaluation of pertussis vaccines require improvement and standardization.

#### Recommendations

Recommendations regarding DTP are the same as those in the generic statements for the monovalent components of this product. They may be summarized as follows:

1. *Diphtheria*—a. Upgrading of surveillance of the diphtheria-immune status of the population is recommended in order to anticipate the possible development of a susceptible population in the future.

b. Efforts should be made to develop an animal model or other laboratory technique for evaluating antigenicity that correlates well with immunogenicity in humans.

c. Public support for the development of a better immunizing agent against diphtheria should be provided. Worthy objectives include not only more immunogenicity but also less reactivity.

2. *Tetanus*—a. Continued efforts should be made to establish, for routine lot-to-lot control, the usefulness of the quantitative technique of the evaluation of tetanus toxoids against the International Standards. This technique is required by the European Pharmacopoeia.

b. Because some current tetanus toxoids appear to have somewhat less antigenic potency than those employed in the past, monitoring of the immune status of a human population sample should be conducted over years in order to ascertain the necessity for continuing booster doses.

3. *Pertussis*—a. Adequate public support should be provided for studies of the pathogenesis of pertussis and the biology of the organism, particularly as related to the immunology of pertussis, the complications of the disease, and the untoward reactions to immunization. The purpose of such studies would be to develop a more effective and safer vaccine.

<sup>1</sup>These three organizations are referred to as National Advisory Committees in other Generic Statements of this Report.

b. Enhanced surveillance of pertussis and the complications of pertussis immunization is strongly recommended.

c. Certain procedures concerning the production and evaluation of pertussis vaccine need to be reevaluated for improvement in precision. These include the mouse weight-gain test, the agglutination test in man, the maximum allowable potency of the human dose, and the inclusion of a clearcut warning on the package label about untoward reactions.

d. Until better laboratory methods for correlating animal models with immunogenicity in man are developed, fractionated vaccines must be tested in field trials as they are developed.

e. Legislation should be enacted that provides public authorization for recompense to individuals who incur rare, but unpredictable and unpreventable, serious reactions to vaccines, including pertussis vaccines.

#### Basis for Classification

The basis for classification of this combined vaccine is the same as that used for the individual components. Since DTP is universally recommended for primary immunization of infants and children, assurance of efficacy is especially germane, and is reasonably obtainable. Serologic evidence of efficacy for the DT components is therefore considered necessary, despite the acknowledged adjuvant effect of pertussis.

#### References

- (1) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," *Morbidity and Mortality Weekly Report*, Suppl. 21(25):4-5, June 24, 1972.
- (2) "Diphtheria—Tetanus—Pertussis," in "Center for Disease Control, United States Immunization Survey: 1975," Health, Education, and Welfare Publication No. (Center for Disease Control), 78-8221:25-30, 1977.
- (3) Center for Disease Control, "Reported Morbidity and Mortality in the United States 1976," *Morbidity and Mortality Weekly Report*, Suppl., Health, Education, and Welfare Publication No. (Center for Disease Control), 77-8241:August 1977.
- (4) Vaccinum Tetanicum Adsorbatum, supplement to Volume III, pp. 174-178, European Pharmacopoeia 1977, Maisonneuve, S.A., 57 Saint Ruffine, France.

#### SPECIFIC PRODUCT REVIEWS

**Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health**

1. *Description.* Contains "purified" diphtheria (10 to 20 Lf per 0.5 mL) and

tetanus toxoids (5 to 10 Lf per 0.5 mL), aluminum phosphate adsorbed, combined with a suspension of *Bordetella pertussis* organisms (8 to 16 opacity units per 0.5 mL). After combination, the potency of each component meets or exceeds Federal requirements. The amount of aluminum phosphate will not exceed 2.5 mg per single human dose (0.5 mL). The product is preserved with 0.1 percent thimerosal. The concentration of formaldehyde may not be greater than 0.01 percent.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for use in children 5 years of age and younger for basic immunization, periodic reinforcing or booster doses, 0.5 mL intramuscularly at 2 to 3 months of age, 3 injections given 4 to 6 weeks apart followed by reinforcing dose 6 to 12 months later and booster prior to entering school.

b. *Contraindications.* Contraindications include acute respiratory infections and corticosteroid or immunosuppressive therapy. If an encephalitic reaction occurs, further immunization should be carried out with DT adsorbed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Data are provided (Ref. 1) to demonstrate immunogenicity when a product which included equivalent amounts of diphtheria and tetanus toxoids and pertussis vaccine but also poliomyelitis vaccine and which had phemerol (benzethonium chloride) rather than thimerosal as a preservative was used in primary immunization. Thirty-eight children age 4 to 6 months and 39 children, age 7 to 12 months, were immunized and bled prior to immunization and 2 weeks after the third injection. Diphtheria and tetanus antitoxin titers and pertussis agglutination titers were satisfactory in all children, as measured in the postimmunization serum. Booster responses were studied in 290 who received 0.2 mL of DTP 13 years after primary immunization; antibody levels were determined at 1 week, 2 weeks and 2, 6, 12, and 24 months. The responses to tetanus and diphtheria were satisfactory in all. Those who failed to show a fourfold or greater increase in antitoxin titers had prebooster levels of >0.01 u per mL. The vaccine used contained less pertussis antigen than recommended, and 25 of 138 (of whom 24 had initial titers of <80) failed to show a fourfold increase in pertussis agglutinin titer.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* When 0.2 mL of DTP was administered to older persons, including

adults (305 subjects), local reactions were severe (46 percent), moderate (30 percent), mild (22 percent), and none in only 2 percent. Severe reactions were associated with mild systemic reactions. Reactogenicity in children is not defined in the submission.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The data of immunogenicity appear satisfactory although the actual immunogen utilized included poliomyelitis vaccine and a different preservative.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

**Diphtheria Toxoid and Pertussis Vaccine Adsorbed Manufactured by Dow Chemical Company**

1. *Description.* No data have been provided by the manufacturer for this product for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment cannot be determined.

4. *Critique.* In the absence of any data from the manufacturer regarding this specific product, and in the absence of any labeling for this product, the Panel must necessarily recommend revocation of this license.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

**Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Dow Chemical Company**

1. *Description.* There are two diphtheria and tetanus toxoids and pertussis vaccine, adsorbed, products